Questions and Answers

Health Canada's Request for submitting confirmation of completion of Step 1 - Risk Assessments for Nitrosamine Impurities (as outlined in the April 14th, 2021 letter)

(Created May 20, 2021)

Background on the objective of this request

Question # 1

Will there be engagement with industry stakeholders, such as a webinar, to discuss Health Canada's proposed approach and answer additional questions?

Health Canada response:

Any additional questions or concerns can be directed to hc.bps.enquiries.sc@canada.ca.

Question # 2

What are the drivers for this request? Is this approach aligned internationally?

Health Canada response:

The main objective for requesting an update on the progress of industry's completion of risk assessments (Step 1) is to gauge the scope of the active pharmaceutical ingredients (APIs) and drug products that may have potential risks of presence of nitrosamine impurities. This will help Health Canada better understand the extent of products that may be affected and to plan for necessary actions for possible drugs of concern and potential drug shortages.

While not all regulators are taking the same approach to follow up on industry's progress, the process of notification for completion of risk assessments that Health Canada has employed is similar to that used by the European Medicines Agency (EMA).

Question # 3

Why has Health Canada changed its direction and is now requesting summaries of all risk assessments performed for all DIN products, regardless of whether nitrosamine impurities or risks of contamination were found? What prompted this change?

Health Canada response:

Health Canada's recent request is intended to capture a high-level summary (Annex 2) of all risk assessments, for each Market Authorisation Holder (MAH). This is not a request for detailed summaries of the risk assessments at this point. As per Question 3 of the "Nitrosamines Questions and Answer document" issued in December 2020, risk assessment documentation should be retained by the MAH, unless nitrosamine impurities are detected in the API, drug product, or both, during the confirmatory testing phase. This will help Health Canada better understand the extent of products that may be affected and to plan for necessary actions for possible drugs of concern and potential drug shortages. Please note that Health Canada may request to review the MAH's risk assessment reports for all products and will request this information directly from the MAH, as deemed necessary.

Question # 4

Is Health Canada planning to take enforcement action based on risk assessment work alone, before confirmatory testing (to be completed by October 1, 2022) has been performed?

Health Canada response:

MAHs should take all necessary steps/actions to complete the risk assessments (if not already completed) as soon as possible and submit the requested information within the requested timelines.

If timelines are not met without an adequate rationale, and/or if no progress is seen, Health Canada may take compliance and enforcement actions as necessary, as per the risk based approach described in the Department's Compliance and enforcement policy for health products (POL-0001). Actions will be determined on a case-by-case basis that considers multiple factors (e.g., risk posed, shortage concerns, medical necessity of the drug product, etc.)

Scope of information to be provided and its use

Question # 5

What are the expectations for risk assessments on dormant, approved and not marketed, and discontinued products?

Health Canada response:

The MAH has a responsibility to prioritize risk assessments based on the knowledge of their product lines and when these will be coming to and remaining on the market. Only products with active DINs, which includes drug products with dormant DINs as well as approved and not marketed drug products but excludes cancelled DINs, are affected by the follow-up letter dated April 14, 2021 on nitrosamine risk assessments as these products can be sold in Canada and may pose a concern to patients and consumers if a risk is identified. Batches of drug products with dormant DINs could still be in distribution if the batches are within their respective expiration periods.

Question # 6

Why is the data on API and Drug Product manufacturers requested? These should not be needed where no risk of presence is identified and could be a lot of work.

Health Canada response:

The data on the API and drug product manufacturing sites is to understand the scope of the drugs that may be affected due to the potential risks of presence of nitrosamine impurities. It is believed that this information should be readily available and accessible by MAHs.

Question # 7

How is Health Canada expecting to use the information gathered on:

- **Whether there was a risk of the presence of nitrosamine**
- **API and Finished Dosage Form manufacturers**
- **Confidentiality of information**

Health Canada response:

Health Canada will be using the information for planning appropriate responses to this global issue (e.g., proactive review of other similar products, targeting operational capacity as needed) and may share the information gathered with other regulatory agencies (e.g., members of the Nitrosamine International Strategic Group) under our confidentiality arrangements, as warranted. Confidential business information (CBI) may be disclosed to eligible persons under specific circumstances as outlined by Guidance Document - Disclosure of Confidential Business Information under Paragraph 21.1(3)(c) of the Food and Drugs Act (https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/request-disclosure-confidential-business-information/disclosure-confidential-business-information/guidance.html)

Guidance on completing Annex 2

Question # 8

The spreadsheet is asking for areas where a "risk of presence of nitrosamines" is identified. How to address when a nitrosamine impurity could be present but this is proven or unlikely to be mutagenic? Changing the wording to "risk from presence of nitrosamines" would probably cover it.

Health Canada response:

The phrases *"risk of presence of nitrosamines"* and *"risk from presence of nitrosamines"* are believed to largely cover the same intent. At this time, all actual and potential nitrosamine impurities (i.e., compounds containing a N-N=O substructure) should be reported in Annex 2, including those the MAH considers to lack mutagenic potential.

Question # 9

In the Annex 2 excel template, fields are provided for MAHs to identify whether a "risk of presence" of nitrosamine impurities has been identified. As Health Canada has noted in many other contexts, risk assessments are rarely, if ever, binary exercises, but rather risk is determined on a scale of degrees.

a) How a MAH should identify whether to indicate "yes" or "no" in the table?

i. **In various documents and communications, Health Canada refers to "potential" nitrosamine presence. Does "potential" mean possible or probable?**
ii. **Should MAHs only assess factors within MAHs' control that could contribute to nitrosamine impurities/formation?**
   (a) **For instance, if there is no reasonable chance of nitrosamine contamination arising from the API manufacturing, or in the production, distribution or storage, would a response of "no" be appropriate, despite some theoretical risk of nitrosamine species formation at various points in the product lifecycle?**
   (b) **If no risk is identified in the API manufacturing, or in the manufacturing, distribution or storage, but a specific source of possible environmental contamination outside of the MAH's control or other deviation from documented processes could result in production or contamination of nitrosamines in trace amounts, is that a "no" in the summary table?**

b) **Can a MAH rely on the Acceptable Intake levels identified by Health Canada in determining whether there is a "risk of presence" of a nitrosamine impurity? i.e. if any contamination that is reasonably possible would only result in daily nitrosamine levels below the acceptable intake levels, would that be a no "risk of presence" in the summary table?**

Health Canada response:

The results of the Risk Assessment (RA) should indicate whether a risk for nitrosamine presence in the API and/or drug product has been identified. If a risk has been identified, then the MAH should mark their response as "yes". Health Canada is aware that the degree of identified risk for the presence of nitrosamine impurities may vary on a product-by-product basis. A potential risk that is identified may also be termed as a possible risk. The completion of Step 2 (confirmatory testing) provides data on the levels of any nitrosamine impurities and the actual risk to patients and consumers.

The MAHs are expected to conduct a comprehensive RA which includes the risk of nitrosamine formation by factors that are both within and outside of the control of the MAH, including soliciting information from the manufacturer of the API, if necessary. This should also take into account any possible risk of nitrosamine formation over the lifecycle of the drug, as any products on the market should not contain nitrosamine impurities above the acceptable intake (AI).

Should the MAH be aware of any possible nitrosamine formation at any stage of the drug lifecycle, they should answer "yes". The MAH can then provide a rationale to Health Canada as to why they believe that the level of nitrosamines in their product does not carry any increased risk to the consumer. Health Canada will assess the rationale and follow up as necessary.

The MAH cannot rely on Health Canada's AI to determine if there is a risk for the presence of a nitrosamine(s). An identified risk of the presence of nitrosamines would result in a "yes" regardless of presumed levels. The level of nitrosamines detected by confirmatory testing will serve to inform Health Canada of potential action required.

Question # 10

The spreadsheet asks for the "name" of the nitrosamine. How to address for structurally complex nitrosamines? IUPAC name?

Health Canada response:

The chemical name should be provided following the recognized International Union of Pure and Applied Chemistry (IUPAC) or Chemical Abstracts Service (CAS) conventions. Alternatively, if assignment of a chemical name is not possible, a clear representation of the chemical structure could be provided.

Question # 11

How do we add additional comments to the spreadsheet to indicate for instance that the risk is believed to be negligible or that the product has been dormant for many years and we have provided the information to the best of our knowledge?

Health Canada response:

Any comments on negligible risk or dormant products that add additional context can be provided in the last column of the spreadsheet.

Guidance on completing Annex 3

Question # 12

Can Health Canada confirm that providing high-level information about challenges and actions performed would satisfy this request?

Health Canada response:

MAHs are requested to provide a robust rationale explaining the details around the challenges they are facing in allowing them to complete their risk assessments and what actions they will be implementing or have implemented to address them. The acceptability of the responses regarding challenges encountered and actions performed will be assessed upon receipt. Health Canada will use this information to determine if extensions may be granted and if any follow-ups and/or compliance and enforcement actions are necessary.

Question # 13

Can sponsors contact hc.nitrosamines.sc@canada.ca **if they need to request additional time to submit the requested documentation?**

Health Canada response:

MAHs are expected to submit what has been completed by the deadline and explain when the additional requested documentation is expected to be provided along with a rationale for the delay and new timeframe. Given the significance of the potential risks and the extended timelines that have been afforded, requests for extensions for administrative reasons will not be considered justified reasons.

Planned compliance and enforcement activities

Question # 14

How is Health Canada planning on following up with sponsors after the provision of this information?

Health Canada response:

Health Canada will assess the rationale for lack of completion and follow up with the MAH as necessary. Health Canada will also follow up with any MAH that fails to provide completed responses to the letter by the deadline.

The information obtained from this progress report will help Health Canada to follow up as necessary on APIs and drug products of concern that have been identified.

Question # 15

How will POL-0001 be applied in the case where MAH require more time to submit a response to this request, and for sponsors who are continuing to work on risk assessments.

Health Canada response:

MAHs should take all necessary steps/actions to complete the risk assessments as soon as possible and submit the requested information within the requested timelines.

If timelines are not met without an adequate rationale, and/or if no progress is seen, Health Canada may take compliance and enforcement actions as necessary as per the risk based approach described in the Department's Compliance and enforcement policy for health products (POL-0001). Actions will be determined on a case-by-case basis that considers multiple factors (e.g. risk posed, shortage concerns, medical necessity of the drug product, etc.)